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REPLY

To the Editor:

Drs Ferri and De Mattia suggest that our finding of unchanged plasma ET-1 levels during hyperinsulinemic clamp (performed at four glucose concentrations: ~5, 9, 14, and 22 mmol/L) in 23 healthy men may be due to the small number of subjects and concomitant inhibitory effect of glucose on ET-1 release during the hyperglycemic-hyperinsulinemic clamps. As described in the Methods section,[1] the 23 volunteers were divided into four groups, which received insulin at infusion rates of 0 (n = 6), 20 (n = 6), 60 (n = 6), and 400 (n = 5) mU/m^2 for 120 minutes. Then, each of the patients participated in four studies, in which the insulin dose for a given patient was always the same, but the glucose concentration varied as specified above. Thus, under euglycemic conditions (and also during three levels of hyperglycemia), a total of 17 patients (6 + 6 + 5) received insulin as specified above. No significant effect of insulin on plasma ET-1 levels during euglycemia was found (analysis of variance followed by *t* test). The result, therefore, cannot be explained by a small study population. In addition, we measured plasma ET-1 from numerous other subjects during euglycemic-hyperinsulinemic clamp studies and did not find any stimulatory effect of insulin (unpublished results).

The question whether glucose participates in the regulation of ET-1 in vivo or in vitro is an interesting one. In vitro, both increased[2] and decreased[3] release of ET-1 have been reported. In our study, we found no effect of glucose on(1) plasma ET-1 levels in vivo and (2) ET-1 release from human umbilical cord vein endothelial cells in vitro. Neither did hyperglycemia modify the stimulatory effect of insulin on ET-1 release in vitro.

We agree with the proposition of Drs Ferri and De Mattia that the function of vascular endothelium in healthy men as compared with patients with non–insulin-dependent diabetes and obesity may be different. At least diabetes has been shown to damage endothelium. Endothelial dysfunction, which may be defined as an imbalance between endothelial production of vasodilating and vasoconstrictive agents, may involve increased production rate of ET-1, but we feel confident that insulin does not increase ET-1 concentrations in vivo.

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